Amendment to the specification:

Please amend the specification as follows:

At Page 1, lines 5-6, please amend the paragraph "Cross-Reference" as follows:

This application is a continuation application of U.S. Patent Application Serial No: 09/903,461, filed July 11, 2001, now U.S. Patent No: 6,602,669, issued on August 5, 2003, which claims the benefit of priority from U.S. Provisional application No: 60/217,782, filed July 11, 2000.

At Page 1, line 7, please insert the following paragraph, before "Field of the Invention":

This application was supported by a grant from the National Institutes of Health, grant number GM57356. The U.S. government may have certain rights to this invention.

Please amend the paragraph at page 1, line 16 – page 2, line 3 as follows:

The use of gold nanoparticle probes as reporter for detection of biological polymers was first described by W. P. Faulk and G. M. Taylor, who employed the nanoparticles as immunocytochemical probes for surface antigens [~~Immunochemitry~~Immunochemistry, 8, 1081 (1971)]. Since then gold colloids have been widely used for detection of a variety of proteins using electron or light-microscopy to observe the particles [for reviews see Hacker, G. W. in Colloidal Gold; Principles, Methods, and Applications, Vol. 1, Academic Press, Inc. (1998) p 297, and Garzon, S., and Bendayan, M. in Immuno-Gold Electron Microscopy in Virus Diagnosis and Research, Ed. Hyatt, A. D. and Eaton, B. T., CRC Press, Ann Arbor, (1993) p 137]. Recently, applications of gold nanoparticle or cluster conjugates as probes for detection of oligonucleotides and nucleic acids have been suggested [Kidwell, D. A., and Conyers, S. M., U.S. Pat. No. 5,384,265 (1995);

Hainfeld, J. F., et al. U.S. Pat. No. 5,521,289 (1996)] and described [Tomlinson, S., et al., Analytical Biochemistry, 171, 217 (1988); Mirkin et al., Nature, 15, 607 (1996); Storhoff, J. J. et al., J. Am. Chem. Soc., 120, 1959 (1998)].

Please amend the paragraph at page 3, line 21 – page 4, line 3 as follows:

A need ~~exits~~exists for a more sensitive, simpler, and cheaper detection method for polynucleotides arrayed on chips. Progress in detection technology has been made with the use of gold nanoparticle oligonucleotide conjugates as probes and signal amplification by silver ion reduction, which enables assays of polynucleotides of 50 fM concentration to be readily detected [for the methodology, see T. A. Taton, C. A. Mirkin; R. L. Letsinger, Science, 289, 1757 (2000)]. We describe here a discovery that significantly lowers further the target concentration required for assays employing gold nanoparticles and other metallic nanoparticles.

Please amend the paragraphs at page 10, line 11 – page 11, line21 as follows:

The silver stain signal amplification method of the invention depends on the use of nanoparticles-oligonucleotide conjugates or complexes that satisfy certain characteristics. First, the nanoparticles do not stick to the surface of the chip being tested. Ordinary nanoparticles prepared by the citrate reduction method of Frens (Frens, G., Nat. Phys. Sci., 241, 20-22 (1973) are not satisfactory since they bind indiscriminately to the oligonucleotide-derivatized glass plate used as the substrate for these assays. Subsequent silver enhancement then gives false positives as dark areas. Second, the nanoparticles bind to a deposited silver surface such that on subsequent washing, the attached nanoparticles remain bound to the silver area while nanoparticles suspended in solution are cleanly removed. Third, the nanoparticles function as agents to reduce silver ions under silver staining conditions. In practicing this invention, useful nanoparticles are nanoparticles

coated with oligonucleotides linked through sulfur to the surface (nanoparticle oligonucleotide conjugates) such as the ones described in J. J. Storhoff et al., J. Am. Chem. Soc., 120, 1958 (1999) (for a specific example, see conjugate I in Example 1 below) or with natural type oligonucleotides adsorbed to the surface (nanoparticle oligonucleotide complexes) such as conjugate III described in Example 1. Both types of nanoparticles work well in low or moderate salt solution (e.g. up to 0.1 M), but the conjugates containing the sulfur anchor are particularly preferred for tests conducted at high salt concentration, at which the complexes formed by simple adsorption of oligonucleotides are unstable and aggregate. It will be understood by the ordinary skilled artisan that any nanoparticle preparation that meets the criteria listed above are useful as intermediary agents in forming the sandwich assemblies, and the methodology can be applied for the amplification of the silver signal for any target visualized by an initial silver deposition. While gold nanoparticles are particularly preferred, any nanoparticle that ~~catalyze~~catalyzes the reduction of silver can be used including silver and platinum nanoparticles.

The preparation of nanoparticles suitable for use in the practice of the invention, the attachment of oligonucleotides to them, the flatbed scanner technique, and various ~~assays~~ assay formats for the detection of nucleic acids using conventional silver staining are described in co-pending applications Ser. Nos. 09/760,500, filed Jan. 12, 2001; 09/603,830, filed Jun. 26, 2000; 09/344,667, filed Jun. 25, 1999; 09/240,755, filed Jan. 29, 1999; 60/031,809, filed Jul. 29, 1996; 60/176,409; and 60/200,161, filed Apr. 26, 2000; and international application Nos. PCT/US97/12783, filed Jul. 21, 1997; PCT/US00/17507, filed Jun. 26, 2000; and PCT/US01/01 190, filed Jan. 12, 2001, entitled "Nanoparticles Having Oligonucleotides Attached Thereto And Uses Therefor," the entire contents of which are incorporated herein by reference.